

REMARKS

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims.

In the present Reply, claims 2, 3, 9, 10, 16, 17, 22, 25, 28, 29, 30, 37, 38 and 42 have been amended. Claims 5, 12, 19, 24, 27, 31 and 32 were previously canceled without prejudice or disclaimer of the subject matter contained therein. Also, claims 44-63 have been added. Thus, claims 1-4, 6-11, 13-18, 20-23, 25, 26, 28-30 and 33-63 are pending in this application.

No new matter has been added by way of the amendments to the present specification and pending claims. One of skill in the art would understand that typographical errors are being corrected in the present specification. Further, upon reviewing a few sources (explained in more detail below), Applicants have discovered such typographical errors and are making the appropriate changes herein. Similar changes are made to claims 37-38. The amendments to claims 2, 3, 9, 10, 16, 17, 22, 25, 28, 29, 30, 37, 38 and 42 merely delete subject matter. Thus, no new matter has been added.

Further, no new matter has been added by way of new claims 44-63. Support for claims 44-53 is found in the present specification at, e.g., page 5, lines 1-6. Support for new claims 54-63 is found in the Examples and at, e.g., page 4, lines 11+.

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Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw the objection and all rejections and allow the currently pending claims.

Claim Objection Under 37 C.F.R. § 1.75

Claim 28 stands objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 22. Applicants respectfully traverse.

The Markush group of the acidic polysaccharide includes "carrageenan" in claim 22, and not in claim 28. Thus, Applicants respectfully submit that the claims are not duplicates of one another. Withdrawal of this objection is respectfully requested

Further, Applicants thank the Examiner for the reminder of the misspellings present in some of the pending claims. In this regard, Applicants have reviewed *The Merck Index* (2001) for the appropriate spellings of some of the drugs listed in claims 37 and 38, as well as in the present specification. Since these changes have been made herein, Applicants respectfully request the Examiner to consider Applicants' changes. Applicants are further attaching excerpts from the mentioned sources that show the correct spellings of the various medicines.

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Issues Under 35 U.S.C. § 112, Second Paragraph

Claims 3, 10 and 17 stand rejected under 35 U.S.C. § 112, second paragraph, for asserted reasons of indefiniteness. Applicants respectfully traverse and respectfully refer the Examiner to the scope of the claims as presented herein. The disputed language no longer appears in these claims. Thus, withdrawal of this rejection is respectfully requested.

Issues under 35 U.S.C. § 102(b) & § 102(e)

Claims 1-3, 7-10, 14-17, 21 and 43 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Drug Information for Vantin® (Physician's Desk Reference (1995); newly cited; hereinafter "Drug Information").

Claims 1-2, 6-9, 13-16, 20-22, 25, 28-30 and 39-43 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Diehl (U.S. Patent No. 5,612,026; also newly cited; hereinafter "Diehl '026").

Applicants respectfully traverse, and reconsideration and withdrawal of these rejections are respectfully requested.

Applicants note that the previous rejections have been overcome, and that the instant rejections are new (see page 7 of the Office Action as well).

Distinctions over the Drug Information reference

The present invention is directed to a basic medicine and acidic polysaccharide being in a medicinal composition, where these ingredients are in intimate contact in order to form an electric interaction and thus prevent the basic medicine from dissolving in saliva. Such features are missing in the cited Drug Information reference. Specifically, the Examiner refers to, in part, the ingredients of cefpodoxim and carrageenan described in the Drug Information reference. However, any use of carrageenan in Drug Information is in the oral suspension (and not in, e.g., a tablet). When used in an oral suspension, as disclosed in the cited reference, carrageenan is a dispersing agent or a gelling agent. In other words, when suspended in water, there is no prevention of the unpleasant taste of the basic medicine as instantly claimed. Further, Drug Information does not disclose the claimed electric interaction.

Thus, Applicants respectfully submit that this rejection has been overcome since "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or

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inherently described, in a single prior art reference." See *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants further note that the mentioned claimed features are not discussed in the Office Action. Thus, because of the lack of disclosure of all features as instantly claimed (e.g., electric interaction; prevention of the unpleasant taste of the medicine), the rejection in view of Drug Information is overcome.

Further, Applicants respectfully submit that the Drug Information reference further fails to disclose a tablet containing carrageenan. An oral suspension is merely described, which does not prevent the unpleasant taste of the basic medicine. In this regard, Applicants respectfully refer the Examiner to the scope of new claims 54-63.

Also, with regard to the disputed method claims (e.g., instantly pending claim 8), there is no disclosure in Drug Information of mixing or blending the claimed ingredients. Instead, the Drug Information reference merely discloses an oral suspension that contains (not mixes) a medicine and agents. In addition, Drug Information does not disclose the claimed electric interaction. Thus, the rejection of the pending method claims is overcome for these additional reasons.

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Accordingly, in light of the above comments, reconsideration and withdrawal of this rejection under § 102(b) are respectfully requested.

Distinctions over the Diehl '026 reference

The cited Diehl '026 reference merely describes an anion-exchanging resin with xanthan gum. Still, there is no description in Diehl '026 of the claimed electric interaction. Further, xanthan gum is deleted from the claims. Thus, this rejection has been overcome. Reconsideration and withdrawal of this rejection are respectfully requested.

Issues Under 35 U.S.C. § 103(a)

Claims 3-4, 10-11, 17-18, 23, 26 and 35-38 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Diehl '026 in view of Drug Information. Further, claims 1-4, 6-11, 13-18, 20-23, 25-26, 28-30 and 33-43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Tai (U.S. Patent No. 5,013,557; hereinafter "Tai '557"). Applicants respectfully traverse both rejections, and reconsideration and withdrawal thereof are respectfully requested.

Distinctions over the Combination of Diehl '026 & Drug Information

As mentioned, the cited primary reference of Diehl '026 merely describes an anion-exchanging resin with xanthan gum and fails to describe or suggest the claimed electric interaction. Further, xanthan gum is deleted from the claims.

Also as mentioned, the cited secondary reference of Drug Information merely describes using carrageenan as a dispersing or gelling agent in an oral suspension (and not in, e.g., a tablet). Drug Information fails to disclose any prevention of the unpleasant taste of the basic medicine, and/or the electric interaction as instantly claimed. The present invention is patentably distinct in that upon oral administration, the electric interaction is produced which masks the bitter taste of the basic medicine.

Thus, even when combined (whether appropriate or not), the cited combination fails to disclose, e.g., the claimed electric interaction. Therefore, a *prima facie* case of obviousness has not been established since there is no disclosure of all claimed features, even when Diehl '026 is combined with the Drug Information reference. See *In re Vaeck*, 947 F.2d, 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); see also *In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). Accordingly, this rejection has been overcome.

Applicants also submit that the requisite motivation is missing. The Examiner refers to how it would be obvious to the skilled artisan "to have substituted one basic active agent for the other in order to benefit from the masking properties for more medications with unpleasant taste" (at page 5 of the Office Action). Diehl '026 focuses on liquid (drink mix) compositions using xanthan gum for reducing serum cholesterol levels (see Abstract; Col. 2, lines 26+). In this regard, replacing the key or essential xanthum gum in Diehl '026 with another polysaccharide gum or ingredient would destroy the intended function of Diehl '026. Applicants note that if a proposal for modifying the cited reference in an effort to attain the claimed invention causes the reference to become inoperable or destroys its intended function, then the requisite motivation to make the modification would not have existed. See *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Since the asserted combination of Diehl '026 and the secondary reference of Drug Information means the alteration of key ingredient(s) in the primary reference of Diehl '026, Applicants respectfully submit that the requisite motivation is lacking and that this rejection has been overcome.

The same reasoning of destroying the intended function of the primary reference applies if another medicine (e.g., donepezil) replaces the key medicine in Diehl '026 (e.g., cholestyramine), in

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that Diehl '026 is directed to reducing serum cholesterol levels. Applicants respectfully submit that the cited combination is improper for this additional reason.

Applicants further note that no technical evidence has been cited or provided in the Office Action to show that the skilled artisan would stray away from the objective of Diehl '026 directed to reducing serum cholesterol level, or that the basic medicine in Diehl '026 should or could be appropriately replaced. The Diehl '026 reference is directed to "Cholesterol Lowering Drink Mix Compositions" (see title of patent), wherein Drug Information is directed to a specific antibiotic. One of skill in the art, in reviewing a reference mainly directed to reducing serum cholesterol levels, would not refer to a reference that discusses antibiotics. Thus, Applicants respectfully submit that the requisite motivation is lacking for this additional reason. *In re Vaeck*.

Applicants even submit that the two cited references are not in an analogous field of one another. *In re Oetiker*, 24 USPQ2d 1443 (Fed. Cir. 1992) (the reference(s) "must either be in the field of the applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned" (24 USPQ2d at 1445; citing *In re Deminski*, 230 USPQ 313, 315 (Fed. Cir. 1986))). Given the many medical references, Applicants respectfully submit that the same field of endeavor cannot be so

broadly classified to include a reference directed to treating cholesterol, and another reference directed to a description of an antibiotic.

Further, the requisite reasonable expectation of success is lacking since "Obviousness requires one of ordinary skill in the art have a reasonable expectation of success as to the invention—'obvious to try' and 'absolute predictability' are incorrect standards." *Velander v. Garner*, 68, USPQ2d 1769, 1784 (Fed. Cir. 2003) (citing *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673 (Fed. Cir. 1988)). In this regard, Applicants respectfully submit that the asserted combination means any reference broadly or generically describing a medicine could be combined. However, such a reasoning equals an "obvious to try" rationale and is improper for an analysis of patentability under § 103(a). See *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1599 (CAFC 1988) (In *In re Fine*, the CAFC reversed the BPAI by stating: "The Board reiterated the Examiner's bald assertion that 'substitution of one type of detector for another in the system of Eads would have been within the skill of the art,' but neither of them offered any support for or explanation of this conclusion.") (emphasis added); see also *In re Deuel*, 34 USPQ2d 1210, 1216 (CAFC 1995) (where the court states: "Obvious to try" has long been held not to constitute obviousness. A general incentive does not make obvious a

particular result, nor does the existence of techniques by which those efforts can be carried out") (citing *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680-1681 (CAFC 1988)). Accordingly, Applicants respectfully submit that this rejection is improper for this reason as well, wherein the reasonable expectation of success is lacking.

Based on the above comments, reconsideration and withdrawal of this rejection are respectfully requested.

Distinctions over the Modification of Tai '557

The Office Actions states that although Tai '557 does not exemplify compositions containing a basic medicine and an acidic polysaccharide, that Tai '557 does "teach mixing a medicine with unpleasant taste with a polysaccharide such as carrageenan to mask the taste..." (see page 6, second paragraph of the Office Action).

The cited Tai '557 reference shows a spraying-dried product including sucralfate (see Abstract; Col. 4, lines 59+; see also the various claims in the reference). More specifically, it is seen in the Tai '557 reference that the unpleasant taste-masking action is caused by a matrix imposed on microcapsules (B), referred to in column 5 or in its claim 9 at column 25. The matrix (B) includes sugar alcohols as a bulking sweet agent (claim 15), and a hydrophobic lubricating agent (see, e.g., claim 1). The spraying-

dried product delivers the medicine component slowly in the mouth out of the outer layer because of the hydrophobic lubricating agent. Thus, the (sweet) bulking agent is delivered in the mouth before the medicine component, which masks the unpleasant taste of the medicine component. This is not the present invention as claimed.

In the present invention, upon oral administration, the electric interaction is produced which masks the bitter taste of the basic medicine. The cited Tai '557 reference fails to show the combination of the instantly claimed invention, as well as the claimed electric interaction.

Further, though the Office Action mentions how Tai '557 fails to exemplify compositions containing a basic medicine and an acidic polysaccharide, Applicants submit that this is the instantly claimed composition and that this is a significant deficiency of the Tai '557 reference. *In re Vaack*.

Applicants also submit that the requisite motivation in order to achieve the present invention is lacking, as claimed, since features such as the claimed electric interaction is not seen or suggested anywhere in disclosure of Tai '557. Thus, Applicants respectfully submit that the instantly claimed compositions are patentably distinct from the spraying-dried product of Tai '557.

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Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eugene T. Perez (Reg. No. 48,501) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

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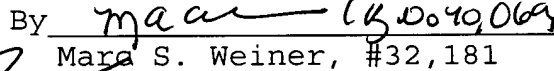
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Pursuant to 37 C.F.R. § 1.17 and 1.136(a), Applicants respectfully petition for a three (3) month extension of time for filing a response in connection with the present application. The required fee of \$1020.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments:

- Excerpts from *The Merck Index* (2001)

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

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2001

d-Form. Crystals from petr ether, mp 136.5-137.5° (sintering). $[\alpha]_D^{25} +98.9^\circ$ (methanol).

l-Form. Crystals from petr ether, mp 136.5-137.5° (sintering). $[\alpha]_D^{25} -101.9^\circ$ (methanol).

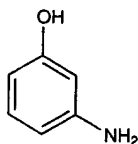
dl-Form hydrochloride. $C_{19}H_{24}N_2O.HCl$. Slightly deliquescent leaflets from alcohol + ether, dec 190-191°. Bitter taste. Soluble in water, alcohol. A 1% aq soln has a pH of 6.8. LD₅₀ in mice (mg/kg): 34.7 i.v.; 396 orally (Cazort).

dl-Form acid sulfate. Centrine. $C_{19}H_{24}N_2O.H_2SO_4$; mol wt 394.49. Deliquescent crystals from isopropanol + ethyl acetate, mp 185-187°. The commercial medicinal grade, mp 178-181°. Bitter taste. uv max (1% H_2SO_4): 258.5 nm ($A_{1cm}^{1\%}$ 10.3); min: 249 nm. Freely sol in water, alc. Very slightly sol in chloroform. Practically insol in ether. pH of 2.5% aq soln 1.3-2.2.

THERAP CAT: Antispasmodic.

THERAP CAT (VET): Antispasmodic; antiemetic.

459. m-Aminophenol. [591-27-5] 3-Amino-1-hydroxybenzene; 3-hydroxyaniline. C_6H_7NO ; mol wt 109.13. C 66.04%, H 6.47%, N 12.83%, O 14.66%. Manuf by reduction of *m*-nitrophenol: Freifelder, Robinson, US 3079435 (1963 to Abbott). Toxicity study: Koelzer, Giesen, Z. *Naturforsch.* 6b, 183 (1951).



Crystals, mp 122-123°. Sol in 40 parts cold water, freely in hot water, alcohol, ether, amyl alcohol; slightly in benzene, very slightly in petr ether. LD₅₀ i.p. in mice: 4.5 mg/20g (Koelzer, Giesen).

USE: Dye intermediate, manuf *p*-aminosalicylic acid.

460. o-Aminophenol. [95-55-6] 2-Aminophenol; 2-amino-1-hydroxybenzene; 2-hydroxyaniline. C_6H_7NO ; mol wt 109.13. C 66.04%, H 6.47%, N 12.83%, O 14.66%. Manuf by reduction of *o*-nitrophenol: Freifelder, Robinson, US 3079435 (1963 to Abbott).

Crystals, rapidly becoming brown, mp 170-174°; sublimes. One gram dissolves in 50 ml cold water, 23 ml alcohol; freely soluble in ether, very slightly in benzene. *Keep tightly closed and protected from light.*

Hydrochloride. $C_6H_7NO.HCl$. Crystals readily becoming gray on exposure to light. Freely sol in water or alcohol.

USE: Manuf azo and sulfur dyes; dyeing furs and hair. Hydrochloride used in dyeing fur, hair, leather, etc.

461. p-Aminophenol. [123-30-8] *p*-Hydroxyaniline; 4-amino-1-hydroxybenzene; Azol; Rodinal; Unal; Ursol P. C_6H_7NO ; mol wt 109.13. C 66.04%, H 6.47%, N 12.83%, O 14.66%. Usually prepd by the reduction of *p*-nitrophenol: BIOS Final Report 986; Freifelder, Robinson, US 3079435 (1963 to Abbott).

Orthorhombic plates from water. *Deteriorates under the influence of air and light.* mp 189.6-190.2°. The commercial product is usually pink, mp 186°. Can be sublimed at 0.3 mm and 110° without decompn. bp₇₆₀ 284° (decompn); bp_{8.0} 167°; bp_{3.0} 150°; bp_{0.3} 130.2°. Kb at 15° = 6.6×10^{-9} . Forms salts with acids and bases. Soly in water: 0.39% at 13°; 0.65% at 24°; 0.80% at 30°; 1.5% at 50°; 4.7% at 80°; 8.5% at 96°. Soly in ethyl methyl ketone: 9.3% at 58.5°; in abs ethanol: 4.5% at 0°. Practically insol in benzene, chloroform.

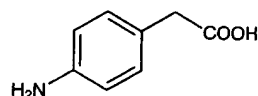
Hydrochloride. $C_6H_7NO.HCl$. Cryst powder; gradually becomes darker. Decomp about 306°. Very sol in water; sol in alc.

Caution: May cause skin sensitization, dermatitis. Inhalation can cause asthma, methemoglobin formation.

USE: Photographic developer; intermediate in the manufacture of sulfur and azo dyes; in dyeing furs and feathers.

462. p-Aminophenylacetic Acid. [1197-55-3] 4-Aminobenzoic acid; *p*-amino- α -toluic acid. $C_8H_7NO_2$; mol wt

151.16. C 63.57%, H 6.00%, N 9.27%, O 21.17%. Prepd by the reduction of *p*-nitrophenylacetic acid with hydrogen sulfide in the presence of ammonia: G. R. Robertson, *Org. Syn. coll. vol. I*, 52 (2nd ed., 1941).



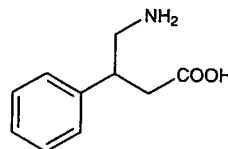
Plates, leaflets from water, mp 199-200° (dec). Moderately sol in hot water; sol in alcohol, in alkalis.

Hydrochloride. $C_8H_7NO_2.HCl$. Rods from HCl, freely sol in water, sol in alcohol (about 3% w/w).

Ethyl ester. $C_{10}H_{13}NO_2$. Platelets from water, mp 51°.

N-Benzoyl deriv. Needles from alcohol, mp 205-206°.

463. 4-Amino-3-phenylbutyric Acid. [1078-21-3] β -(Aminomethyl)benzenepropanoic acid; β -(aminomethyl)hydrocinnamic acid; 4-amino-3-phenylbutanoic acid; β -phenyl- γ -aminobutyric acid; phenygam; PhGABA; Phenigam; Fenigam; Phenigama; Fenigama. $C_{10}H_{13}NO_2$; mol wt 179.22. C 67.02%, H 7.31%, N 7.82%, O 17.85%. Prepn starting with α,γ -diamino- β -phenylpropane: Jackson, Kenner, *J. Chem. Soc.* 1928, 1657. Alternate prepn: Cologne, Pouchol, *Bull. Soc. Chim. France* 1962, 598. Pharmacology: R. A. Khaunina, *Bull. Exp. Biol. Med.* 57, 52 (1964). Structure-activity studies: *idem, Farmakol. Toksikol.* 31, 202 (1968). Activity studies of the isomers: *idem, Byull. Eksp. Biol. Med.* 72, 49 (1971), *C.A.* 76, 81208t (1972).



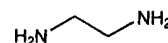
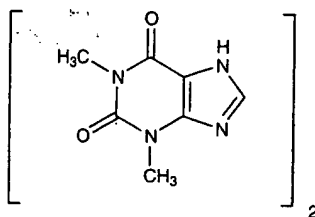
mp 250-253° (dec).

Hydrobromide. [103095-38-1] $C_{10}H_{13}NO_2.HBr$. Irregular platelets from benzene, mp 114°.

Hydrochloride. [3060-41-1] LD₅₀ in mice, rats (mg/kg): 900, 700 i.p. (Khaunina, 1964).

THERAP CAT: Mood elevator, tranquilizer.

464. Aminophylline. [317-34-0] 3,7-Dihydro-1,3-dimethyl-1*H*-purine-2,6-dione compd with 1,2-ethanediamine (2:1); theophylline compd with ethylenediamine; theophylline ethylenediamine; theophyllamine; Afonilum; Aminodur; Cardophyllin; Euphyllina; Pecram; Phyllocontin; Phyllotemp; Planphylline; Pulmovet; Tefamin. $C_{16}H_{24}N_{10}O_4$; mol wt 420.43. C 45.71%, H 5.75%, N 33.32%, O 15.22%. Prepn: Grüter, US 919161 (1909 to Byk). Toxicity data: C. R. Thompson, M. R. Warren, *J. Lab. Clin. Med.* 31, 1337 (1946). Comprehensive description: K. D. Thakker, L. T. Grady, *Anal. Profiles Drug Subs.* 11, 1-44 (1982). Reviews of clinical experience: J. A. Stirt, S. F. Sullivan, *Anesth. Analg.* 60, 587-602 (1981); A. G. Perry, *AACN Clin. Issues* 6, 297-306 (1995).



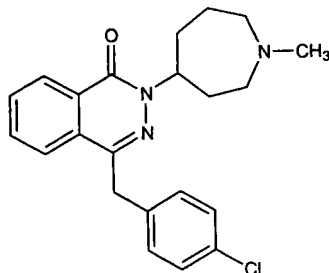
Occurs as the dihydrate. White or slightly yellowish granules or powder. Slight ammoniacal odor. Bitter taste. Gradually absorbs carbon dioxide from the air and becomes incompletely sol due to liberation of theophylline. One gram dissolves in about 5 ml water, but the soln may become turbid on standing.

Monoclinic prismatic needles, mp 106.5°. Distills above 360° with partial anhydride formation. bp₁₀₀ 286.5°; bp₅₀ 265°; bp₁₅ 237°; bp₁₀ 225°. d₄^{10.6} 1.0291. One liter of water dissolves 1.0 g at 1.0°; 2.4 g at 20°; 8.2 g at 50°; 22 g at 65°. Freely sol in boiling water, in alcohol. 1000 g of ether dissolves 18.8 g at 11° and 26.8 g at 15°. pK₁ (25°) 4.53; pK₂ 5.33.

Dimethyl ester. C₁₁H₂₀O₄. Liquid, d₄²⁰ 1.0026. mp -3.9° bp₈ 140°.

THERAP CAT: Antiacne.

909. Azelastine. [58581-89-8] 4-[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone; 4-(p-chlorobenzyl)-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone; 4-(p-chlorobenzyl)-2-(N-methylperhydroazepin-4-yl)-1(2H)-phthalazinone. C₂₂H₂₄ClN₃O; mol wt 381.91. C 69.19%, H 6.33%, Cl 9.28%, N 11.00%, O 4.19%. Orally active H₁-histamine receptor antagonist. Prepn: BE 778269; D. Vogelsang *et al.*, US 3813384 (1972, 1974 both to Asta-Werke AG). Synthesis and x-ray structure determ: G. Scheffler *et al.*, *Arch. Pharm.* 321, 205 (1988). Pharmacology: K. Tasaka, M. Akagi, *Arzneimittel-Forsch.* 29, 488 (1979). Pharmacology and toxicology: H. J. Zechel *et al.*, *ibid.* 31, 1184 (1981). Series of articles on pharmacokinetics, pharmacology and toxicology: *ibid.* 1184-1238. Mechanism of action studies: N. Chand *et al.*, *Int. J. Immunopharmacol.* 7, 833 (1985); *idem*, *Br. J. Pharmacol.* 87, 443 (1986). HPLC determ in plasma: J. Pivonka *et al.*, *J. Chromatog.* 420, 89 (1987). Clinical evaluations in asthma: H. Magnussen, *Chest* 91, 855 (1987); M. K. Albazzaz, K. R. Patel, *Thorax* 43, 306 (1988).



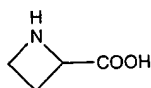
Oil. Sol in methylene chloride.

Monohydrate. C₂₂H₂₄ClN₃O·H₂O. Crystals from alcohol/water. Two distinct crystal forms have been identified (Scheffler).

Hydrochloride. [79307-93-0] A-5610; E-0659; W-2979M; Allergodil; Astelin; Azeptin; Optilast; Rhinolast. C₂₂H₂₄ClN₃·O·HCl; mol wt 418.37. Crystals from alcohol, mp 225-229°. LD₅₀ in male, female mice, male, female rats (mg/kg): 36.5, 35.5, 26.9, 30.3 i.v.; 56.4, 42.8, 43.2, 46.6 i.p.; 63.0, 54.2, 66.5, 59.6 s.c.; 124, 139, 310, 417 orally (Zechel).

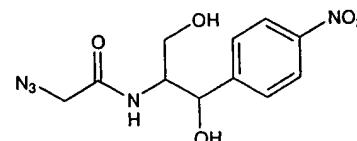
THERAP CAT: Antihistaminic.

910. 2-Azetidinecarboxylic Acid. [2517-04-6] C₄H₇NO₂; mol wt 101.10. C 47.52%, H 6.98%, N 13.85%, O 31.65%. From *Convallaria majalis* L. (lily-of-the-valley) and *Polygonatum officinale* Moench., *Liliaceae*: Fowden, *Biochem. J.* 64, 323 (1956); Fowden, Bryant, *ibid.* 70, 626 (1958). Structure: Virtanen, *Angew. Chem.* 67, 619 (1955); Fowden, *loc. cit.* Biosynthesis: Linko, *Acta Chem. Scand.* 12, 101 (1958); Fowden, Bryant, *Biochem. J.* 71, 210 (1959); Fowden, *ibid.* 71, 643 (1959); Leete, *J. Am. Chem. Soc.* 86, 3162 (1964). Shows growth-inhibitory activity on cultures of *Escherichia coli* and on germinating seeds of different species in which it does not normally occur; Fowden, Richmond, *Biochim. Biophys. Acta* 71, 459 (1963). Acts as a proline analog where a stoichiometric replacement of proline occurred with production of abnormal proteins having impaired biological activity: Peterson, Fowden, *Nature* 200, 148 (1963).



Crystals from 95% hot methanol, discolors at 200° and cens until 310° when heating stopped. [α]_D²⁰ -108° (c = 1.6 in ethyl acetate). pH 7.1. Sol in water up to 2%. Unstable to mineral acids. Soluble in cold and hot water. Insoluble in abs ethanol.

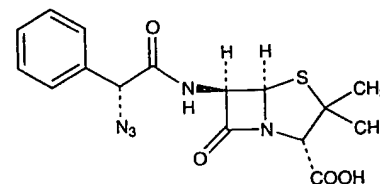
911. Azidamfenicol. [13838-08-9] 2-Azido-N-[2-droxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]acetamid (-)-threo-1-p-nitrophenyl-2-azidoacetaminopropan-3-diol; D-(-)-threo-2-azidoacetamido-1-p-nitrophenyl-1,3-penediol; azidoamphenicol; Berlicetin; Leukomycin-N; Posicol; Thilocanfol. C₁₁H₁₃N₅O₅; mol wt 295.25. C 44.75%, 4.44%, N 23.72%, O 27.09%. Semi-synthetic antibiotic related to chloramphenicol, q.v. Prepn: Meiser, Domagk, US 288 (1959 to Bayer).



Crystals from ethylene chloride, mp 107°. [α]_D²⁰ -20° (c = 1.6 in ethyl acetate). pH 7.1. Sol in water up to 2%.

THERAP CAT: Antibacterial.

912. Azidocillin. [17243-38-8] (2S,5R,6R)-6-[[[(2R)-dophenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azoclo[3.2.0]heptane-2-carboxylic acid; α-azidobenzylpen: 6-[D-α-azidophenylacetamido]penicillanic acid; SPC-97D; 2351. C₁₆H₁₇N₅O₄S; mol wt 375.41. C 51.19%, H 4.51%, 18.66%, O 17.05%, S 8.54%. Semi-synthetic antibiotic related to penicillin. Prepn: B. O. H. Sjöberg, B. A. Ekström, *Acta Chem. Scand.* 19, 281 (1965). Pharmacology: *idem*, *Acta Chem. Scand.* 19, 281 (1965). Pharmacology: *idem*, *Acta Chem. Scand.* 19, 281 (1965). Chemistry: Sjöberg *et al.*, *ibid.* 560. Me studies: Ramsey *et al.*, *Arzneimittel-Forsch.* 22, 1962 (1972).

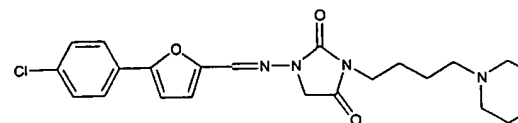


Sodium salt. [35334-12-4] Globacillin; Longatren; lin. C₁₆H₁₆N₅NaO₄S; mol wt 397.39.

THERAP CAT: Antibacterial.

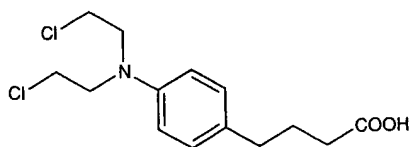
THERAP CAT (VET): Antimicrobial. (In mastitis, as supplement).

913. Azimilide. [149908-53-2] 1-[[[5-(4-chlorophenyl)-2-furanyl]methylene]amino]-3-[4-(4-methylperazinyl)butyl]-2,4-imidazolidinedione. C₂₃H₂₈ClN₅O; mol wt 457.96. C 60.32%, H 6.16%, Cl 7.74%, N 15.10%, 10.48%. Potassium channel blocker. Prepn: S. S. Pelo, WO 93 04061 (1993 to Procter & Gamble); C.-N. Yu *et al.*, WO 93 04061 (1993 to Procter & Gamble); C.-N. Yu *et al.*, WO 93 04061 (1993 to Procter & Gamble). Clinical pharmacology: A. Corey *et al.*, *J. Clin. Pharmacol.* 37, 946 (1997). trial to improve post-infarct survival: A. J. Camm *et al.*, *Cardiol.* 81, Suppl. 6A, 35D (1998). Review of electrophysiological properties and pharmacology: R. Karam *et al.*, *ibid.* 46D.



Dihydrochloride. [149888-94-8] NE-10064; Stedi. H₂₈ClN₅O₃·2HCl; mol wt 530.88. Crystals from ethan THERAP CAT: Antiarrhythmic (class III).

C. J. Ross, *Biochem. Pharmacol.* 13, 969 (1964). Review of carcinogenicity studies: *IARC Monographs* 9, 125-134 (1975). Comprehensive description: M. Tariq, A. A. Al-Badr, *Anal. Profiles Drug Subs.* 16, 85-118 (1987).



Flattened needles from petr ether, mp 64-66°. Sol in ether. Sol at 20° in 1.5 parts alcohol, in 2.5 parts chloroform, in 2 parts acetone. Practically insol in water. LD₅₀ i.p. in rats: 58.2 µmole/kg (Ross).

Note: This substance has been listed as a known human carcinogen: *Ninth Report on Carcinogens* (PB2000-107509, 2000) p III-21.

THERAP CAT: Antineoplastic.

THERAP CAT (VET): Antineoplastic agent, esp for leukemia.

2084. Chloramine-B. [127-52-6] *N*-Chlorobenzenesulfonamide sodium salt; (*N*-chlorobenzenesulfonamido)sodium; sodium benzenesulfochloramine; Neomagnol. C₆H₅ClN₂NaO₂S; mol wt 213.62. C 33.74%, H 2.36%, Cl 16.60%, N 6.56%, Na 10.76%, O 14.98%, S 15.01%. C₆H₅SO₂NNaCl. Prep'd via benzenesulfonamide: Chattaway, *J. Chem. Soc.* 87, 145 (1905); Cuiban *et al.*, *Pharmazie* 13, 407 (1958).

Trihydrate. Prisms. Soluble in 20 parts of water, more sol in hot water. Sol in 25 parts of ethanol, yielding a turbid soln. Very sparingly sol in ether, chloroform. An aq soln first turns red litmus paper blue, then gradually bleaches it. Gives a red color with phenolphthalein.

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antiseptic (topical).

2085. Chloramine-T. [127-65-1] *N*-Chloro-4-methylbenzenesulfonamide sodium salt; (*N*-chloro-*p*-toluenesulfonamido)sodium; sodium *p*-toluenesulfochloramine; chloramine; Aktiven; Chloraseptine; Chlorazene; Chlorazone; Euclozina; Gansil; Halamid; Mianine; Tochlorine; Tolamine. C₇H₇ClN₂NaO₂S; mol wt 227.65. C 36.93%, H 3.10%, Cl 15.57%, N 6.15%, Na 10.10%, O 14.06%, S 14.09%. *p*-CH₃C₆H₄SO₂NNaCl. Prep'd via *p*-toluenesulfonamide: Chattaway, *J. Chem. Soc.* 87, 145 (1905); Inglis, *J. Soc. Chem. Ind. (London)* 37, 288 (1918); F. J. Welcher, *Organic Analytical Reagents* vol. 4 (Van Nostrand, New York, 1948) pp 316-320.

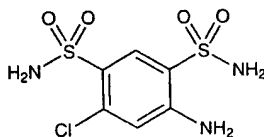
Trihydrate. Prisms. Loses water on drying. Dec slowly on exposure to air. Keep well closed. Fairly sol in water. Practically insol in benzene, chloroform, ether. Dec by alc.

USE: Detection of bromate and halogens, F. J. Welcher, *loc. cit.*

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antiseptic (topical).

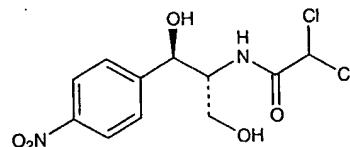
2086. Chloraminophenamide. [121-30-2] 4-Amino-6-chloro-1,3-benzenedisulfonamide; 4-amino-6-chloro-*m*-benzenedisulfonamide; 5-chloro-2,4-bis(sulfonamido)aniline; 6-amino-4-chlorobenzene-1,3-disulfonamide; 5-chloro-2,4-disulfamylaniline; Idorese. C₆H₅ClN₃O₄S₂; mol wt 285.73. C 25.22%, H 2.82%, Cl 12.41%, N 14.71%, O 22.40%, S 22.44%. Prep'n: Novello, Sprague, *J. Am. Chem. Soc.* 79, 2028 (1957); Novello, US 2809194; US 2965655; US 2965656 (1957, 1960, 1960 all to Merck & Co.); Novello *et al.*, *J. Org. Chem.* 25, 965 (1960).



Crystals from aq ethanol, mp 251-252°. uv max (ethanol): 223.5-224.5, 265-266, 312-314 nm (ε 41776, 18633, 3874). Slightly sol in water; more freely sol in alkalis.

THERAP CAT: Diuretic.

2087. Chloramphenicol. [56-75-7] 2,2-Dichloro-*N*-(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethylacetamide; *D*-threo-*N*-dichloroacetyl-1-*p*-nitrophenyl-2-amino-1,3-propanediol; *D*(-)-threo-2-dichloroacetamido-1-*p*-nitrophenyl-1,3-propanediol; *D*-threo-*N*-(1,1'-dihydroxy-1-*p*-nitrophenylisopropyl)dichloroacetamide; Ak-Chlor; Amphicol; Anaceticin; Aquamycetin; Chemicitina; Chloramex; Chlorasol; Chloricol; Chlorocid; Chloromycetin; Chloroptic; Cloramfen; Clorocyn; Enicol; Farmicetina; Fenicol; Intramycetin; Kernicetine; Leukomycin; Micoclorina; Mychel; Mycinol; Novomycetin; Ophthochlor; Pantovernil; Paraxin; Quemicetina; Ronphenil; Sintomicetina; Sno Phenicol; Synthomycetin; Tevcocin; Tifomycine; Veticoveton. C₁₁H₁₂Cl₂N₂O₅; mol wt 323.13. C 40.89%, H 3.74%, Cl 21.94%, N 8.67%, O 24.76%. Broad spectrum antibiotic obtained from cultures of the soil bacterium *Streptomyces venezuelae*: Bartz, *J. Biol. Chem.* 172, 445 (1948); Gottlieb *et al.* *J. Bact.* 55, 409 (1948); Ehrlich *et al.*, *ibid.* 56, 467 (1948). Isol from the moon snail, *Lunatia heros*: C. A. Price *et al.*, *J. Antibiot.* 34, 118 (1981). Structure: Rebstock *et al.*, *J. Am. Chem. Soc.* 71, 2458 (1949). Synthesis: Controulis *et al.*, *ibid.* 246, Long, Troutman, *ibid.* 2469, 2473. See also US 2483871; US 2483884; US 2483892. Alternate synthesis: Ehrhart *et al.*, *Be* 90, 2088 (1957); GB 795131; GB 796901 C.A. 53, 2161 (1957) (both to Chinoïn); US 2839577 (1958 to Chinoïn). Review at evaluation of toxicity studies: *IARC Monographs* 10, 85-145 (1976). Review of pharmacology and clinical efficacy: Shalit, M. I. Marks, *Drugs* 28, 281-291 (1984). Comprehensive description: D. Szulczewski, F. Eng, *Anal. Profiles Drug Sub.* 4, 47-90 (1975); A. A. Al-Badr, H. A. El-Obeid, *ibid.* 15, 70-760 (1986). Reviews: Hahn in *Antibiotics*, vol. 1, D. Gottlieb, P. D. Shaw, Eds. (Springer-Verlag, New York, 1967) pp 30-330; Pestka, *ibid.* vol. 3, J. W. Corcoran, F. E. Hahn, Eds. (1973) pp 370-395; O. Pongs, *ibid.* vol. 5, pt. 1, F. E. Hahn, Ed. (1977) pp 26-42.



Needles or elongated plates from water or ethylene dichloride, mp 150.5-151.5°. Sublimes in high vacuum. [α]_D²⁵ +18.6° (c 4.86 in ethanol). [α]_D²⁵ -25.5° (ethyl acetate). uv max: 278 nm (E_{1cm}^{1%} 298). Soly (25°) in water: 2.5 mg/ml; in propylene glycol: 150.8 mg/ml. Very sol in methanol, ethanol, butanol, ethyl acetate, acetone. Fairly sol in ether. Insol in benzene, petr ether, vegetable oils. Soly in 50% acetamide soln about 5%. Additional soly data: Weiss *et al.*, *Antibiot. Chemother.* 7, 10 (1957). Aq solns are neutral. Neutral and acid solns are stable on heating.

Monosuccinate sodium salt. [982-57-0] Globenicol; Ictophenicol. C₁₅H₁₅Cl₂N₂NaO₈; mol wt 445.19. Freely sol in water (about 50% w/w).

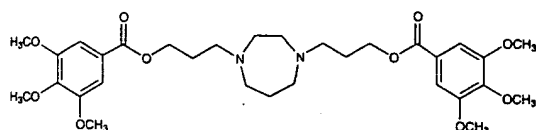
Palmitate. [530-43-8] Chlorambon; Chloropal; Cloroprina. Prep'n: Edgerton, US 2662906 (1953 to Parke, Davis). Structure: Edgerton *et al.*, *J. Am. Chem. Soc.* 77, 27 (1955). Description: Glazko *et al.*, *Antibiot. Chemother.* 2, 234 (1952). Soly data: Weiss *et al.*, *ibid.* 7, 374 (1957). Crystals from benzene, mp 90°. Practically tasteless. [α]_D²⁵ +24.6° (c = 5 in anol). uv max (ethanol): 271 nm (E_{1cm}^{1%} 179). Very slightly sol in water (1.05 mg/ml at 28°); petr ether (0.225 mg/ml). Freely sol in methanol, ethanol, chloroform, ether, benzene.

Monosuccinate arginine salt. [34327-18-9] Chloramphenicol arginine succinate; Paraxin Succinate A. C₂₁H₃₀Cl₂N₄O₈; mol wt 597.41. mp 135-145° (dec.). See *Japan. Med. J.* 7(10), 15 (1970).

Pantothenate calcium complex (4:1). [31342-36-6] Chloramphenicol pantothenate; Pantofenicol. C₆₂H₈₀CaCl₂N₄O₁₀

sodium salt. Dikegulac-sodium; Ro-7-6145; Atrinal. $C_{12}H_{11}NaO_7$; mol wt 296.25. Powder, mp $>300^\circ$. Vapor pressure 25° : $<10^{-10}$ mm Hg. Soly at 20° (g/l): water 590; methanol 3; ethanol 230; chloroform 60; acetone <10 ; hexane <10 ; dihexanone <10 . LD₅₀ in mice, male, female rats (mg/kg): 500, 31000, 18000 orally; LC₅₀ (96 hr) in bluegill sunfish, rainbow trout (ppm): >10000 , >5000 (de Silva). USE: Plant growth regulator; herbicide.

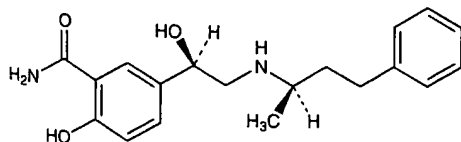
3223. Dilazep. [35898-87-4] 3,4,5-Trimethoxybenzoic acid tetrahydro-1*H*-1,4-diazepine-1,4(5*H*)-diyl-di-3,1-propanediyl ester of 3,4,5-trimethoxybenzoic acid diester with tetrahydro-1*H*-1,4-diazepine-1,4(5*H*)-dipropanol; 1,4-bis[3-(3,4,5-trimethoxybenzoyloxy)propyl]perhydro-1,4-diazepine; *N,N'*-bis[3-(3,4,5-trimethoxybenzoyloxy)propyl]homopiperazine; *N,N'*-(bis- ω -hydroxypropyl)-homopiperazine 3,4,5-trimethoxybenzoate (diester). $C_{31}H_{44}N_2O_{10}$; mol wt 604.69. C 61.57%, H 7.33%, N 4.63%, O 26.46%. pn: GB 1107470 corresp to Arnold *et al.*, US 3532685 68, 1970 both to Asta-Werke). Series of articles on pharmacology and metabolism: *Arzneimittel-Forsch.* 22, 639-666 (72). Toxicology: H. H. Abel *et al.*, *ibid.* 667. Clinical results: Messerich, *Med. Welt.* 1972, 563.



hydrochloride. [20153-98-4] Asta C 4898; Comelian; melian; Labitan. $C_{31}H_{44}N_2O_{10} \cdot 2HCl$; mol wt 677.62. Crystals from ethanol, mp $194-198^\circ$ (monohydrate). LD₅₀ in male rats (mg/kg): 26.6, 19.1 i.v.; 161, 90.1 i.p.; 3740, 150 orally (Abel).

HERAP CAT: Vasodilator (coronary).

3224. Dilevalol. [75659-07-3] 2-Hydroxy-5-[(1*R*)-1-hydroxy-2-[[[(1*R*)-1-methyl-3-phenylpropyl]amino]ethyl]benzyl]; (1*R*)-labetalol; Sch-19927; Dilevalon; Levadil; Unidil. $C_{19}H_{24}N_2O_3$; mol wt 328.40. C 69.49%, H 7.37%, N 3%, O 14.62%. Non-selective β -adrenergic blocker with vasodilating activity; active isomer of labetalol, *q.v.* For prepn acetate see labetalol. Synthesis and preliminary pharmacology: J. E. Clifton *et al.*, *J. Med. Chem.* 25, 670 (1982); E. Gold *et al.*, *ibid.* 1363. Absolute configuration: P. Murray *et al.*, *Acta Crystallogr.* C40, 825 (1984). Adrenoceptor binding properties in comparison with labetalol: E. J. Sybertz *et al.*, *J. Pharmacol. Exp. Ther.* 218, 435 (1981). Antihypertensive and hemodynamic effects in rats and dogs: T. Baum *et al.*, *ibid.* 444; and cardiac effects: J. J. Lynch *et al.*, *ibid.* 239, 719 (86). HPLC determination in biological fluids: K. B. Alton *et al.*, *Chromatog.* 425, 363 (1988). Clinical evaluation in hypertension: J. Soberman *et al.*, *J. Clin. Hypertens.* 3, 271 (1987); J. Wallin *et al.*, *Arch. Intern. Med.* 148, 534 (1988). Symposium on pharmacology and clinical efficacy: *J. Cardiovasc. Pharmacol.* 11, Suppl. 2, S1-S45 (1988).



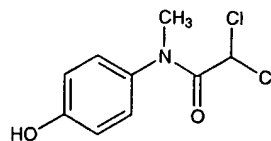
um. $[\alpha]_D -21.7^\circ$.

hydrochloride. [75659-08-4] $C_{19}H_{24}N_2O_3 \cdot HCl$. Polymorphic crystals from ethanol, mp $133-134^\circ$ (dec); mp $192-193.5^\circ$ (c). $[\alpha]_D^{25} -30.6^\circ$ (c = 1.0 in ethanol).

HERAP CAT: Antihypertensive.

3225. Diloxanide. [579-38-4] 2,2-Dichloro-*N*-(4-hydroxyphenyl)-*N*-methylacetamide; 2,2-dichloro-4'-hydroxy-*N*-methyl-anilide; *N*-dichloroacet-4-hydroxy-*N*-methyl-anilide; 4-hydroxy-*N*-methyl-dichloroacetanilide; Entamide. $C_9H_9Cl_2NO_2$;

mol wt 234.08. C 46.18%, H 3.88%, Cl 30.29%, N 5.98%, O 13.67%. Prepn: P. Oxley *et al.*, US 2912438 (1959 to Boots Pure Drug). Spectrophotometric determination in 2-component tablet formulation: S. M. Galal *et al.*, *J. Pharm. Belg.* 46, 315 (1991). Clinical trial of combination with metronidazole, *q.v.*, in amoebiasis and giardiasis: H. Qureshi *et al.*, *J. Int. Med. Res.* 25, 167 (1997). Review of clinical experience: J. B. McAuley *et al.*, *Clin. Infect. Dis.* 15, 464-468 (1992).

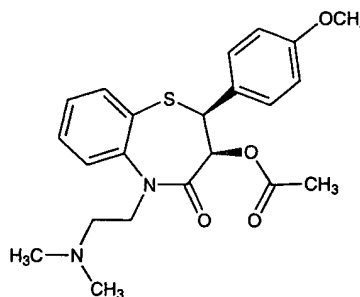


Crystals from ethyl acetate, mp 175° .

Furoate. [3736-81-0] Diloxanide 2-furoic acid ester; Furoamide.

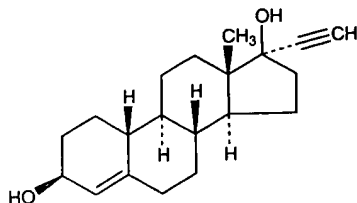
THERAP CAT: Antiamebic.

3226. Diltiazem. [42399-41-7] (2*S*-*cis*)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one; (+)-*cis*-5-[2-(dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one acetate (ester). $C_{22}H_{26}N_2O_4S$; mol wt 414.53. C 63.74%, H 6.32%, N 6.76%, O 15.44%, S 7.74%. Calcium channel blocker with vasodilating activity. Prepn (unspec stereochem): H. Kugita *et al.*, DE 1805714; *idem*, US 3562257 (1969, 1971 both to Tanabe Seiyaku); *idem*, *Chem. Pharm. Bull.* 19, 595 (1971). Resolution of optical isomers: H. Inoue *et al.*, *Yakugaku Zasshi* 93, 729 (1973), *C.A.* 79, 66331w (1974). Stereospecific synthesis: K. Igarashi, T. Honma, DE 3415035; *idem*, US 4552695 (1984, 1985 both to Shionogi). Structure-activity studies: Sato *et al.*, *Arzneimittel-Forsch.* 21, 1338 (1971); T. Nagao *et al.*, *Chem. Pharm. Bull.* 21, 92 (1973). Pharmacology and toxicity: *idem*, *Japan. J. Pharmacol.* 22, 467 (1972). Metabolism: Meshi *et al.*, *Chem. Pharm. Bull.* 19, 1546 (1971). Review of synthesis and pharmacology: H. Inoue, T. Nagao, *Chron. Drug Discovery* 3, 207-238 (1993). Comprehensive description: D. J. Mazzo *et al.*, *Anal. Profiles Drug Subs. Excerpt.* 23, 53-98 (1994). Review of pharmacology and efficacy in angina: M. Chaffman, R. N. Brogden, *Drugs* 29, 387-454 (1985); in hypertension: M. R. Weir, *J. Clin. Pharmacol.* 35, 220-232 (1995). Comparative clinical trial in prevention of complications of hypertension: L. Hansson *et al.*, *Lancet* 356, 359 (2000).



Hydrochloride. [33286-22-5] CRD-401; Adizem; Altiazem; Angizem; Britiazim; Bruzem; Cardizem; Citizem; Deltazen; Dilacor XR; Diladel; Dilpral; Dilrene; Diltzem; Diltzene; Herbesser; Masdil; Tiazac; Tildiem; Zilden. $C_{22}H_{26}N_2O_4S \cdot HCl$; mol wt 450.99. Fine needles from ethanol-isopropanol, mp $207.5-212^\circ$. Odorless, with a bitter taste. $[\alpha]_D^{25} +98.3 \pm 1.4^\circ$ (c = 1.002 in methanol). Freely sol in water, methanol, chloroform, formic acid; slightly sol in abs ethanol. Practically insol in benzene. Insol in ether. LD₅₀ in male, female mice, male, female rats (mg/kg): 61, 58, 38, 39 i.v.; 260, 280, 520, 550 s.c.; 740, 640, 560, 610 orally (Nagao, 1972).

THERAP CAT: Antianginal; antihypertensive; antiarrhythmic (class IV).



Diacetate. [297-76-7] 3β,17β-Diacetoxy-17α-ethynyl-4-estrene; SC-11800; Femulen; Luteonorm; Luto-Metrodiol; Metrodiol. $C_{24}H_{32}O_4$; mol wt 384.51. Crystals from methanol + water, mp ~ 126-127°. $[\alpha]_D -72.5^\circ$ (chloroform).

Diacetate mixture with mestranol. Luteolas; Metrulen; Ovaras; Ovulen.

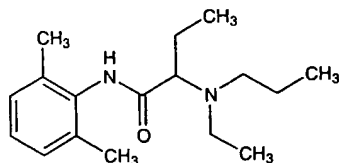
Diacetate mixture with ethinyl estradiol. Conova; Demulen; Miniluteolas.

THERAP CAT: Progestogen; in combination with estrogen as oral contraceptive.

3892. Ethynylbenzene. [536-74-3] Phenylacetylene. C_8H_6 ; mol wt 102.13. C 94.08%, H 5.92%. $C_6H_5C\equiv CH$. Prep'd by dropping β-bromostyrene on molten potassium hydroxide and distilling; Hessler, *Org. Syn.* 2, 67 (1922).

Liquid. d_4^{20} 0.9300. mp -44.8°. bp₇₆₀ 142.4°; bp₉₀ 75°; bp₁₅ 39°. n_D^{20} 1.5489. Insol in water; miscible with alcohol, ether, other organic solvents.

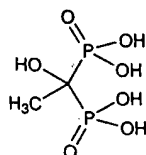
3893. Etidocaine. [36637-18-0] *N*-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide; 2-(ethylpropylamino)-2',6'-butyroxylidide. $C_{17}H_{28}N_2O$; mol wt 276.42. C 73.87%, H 10.21%, N 10.13%, O 5.79%. Prepn: H. J. F. Adams *et al.*, *DE 2162744*; *eidem*, *US 3812147* (1972, 1974 both to Astra). Activity and toxicity studies: *eidem*, *J. Pharm. Sci.* 61, 1829 (1972).



Hydrochloride. [36637-19-1] W-19053; Duranest. $C_{17}H_{28}N_2O.HCl$; mol wt 312.89. Crystals from abs ethanol-ether and isopropanol-isopropylether, mp 203-203.5°. LD₅₀ in female mice (mg/kg): 6.7 i.v.; 99 s.c. (Adams, 1972).

THERAP CAT: Anesthetic (local).

3894. Etidronic Acid. [2809-21-4] (1-Hydroxyethylidene)bisphosphonic acid; (1-hydroxyethylidene)diphosphonic acid; ethane-1-hydroxy-1,1-diphosphonic acid; Dequest 2010; Fostex P. $C_2H_8O_7P_2$; mol wt 206.03. C 11.66%, H 3.91%, O 54.36%, P 30.07%. Bisphosphonate antiresorptive agent. Prepn: H. von Baeyer, K. A. Hofmann, *Ber.* 30, 1973 (1897); and characterization of the acid and disodium salt: F. Kasperek, *Monatsh.* 99, 2016 (1968); B. Blaser *et al.*, *Z. Anorg. Allgem. Chem.* 381, 247 (1971). Use as detergent builder: F. L. Diehl, *US 3159581* (1964 to Proctor & Gamble). Determin in pharmaceutical formulations: E. W. Tsai *et al.*, *J. Pharm. Biomed. Anal.* 11, 513 (1993). Symposium on clinical efficacy in malignancy-related hypercalcemia: *Am. J. Med.* 82, Suppl 2A, 1-78 (1987). Review of pharmacology and therapeutic efficacy in resorptive bone disease: C. J. Dunn *et al.*, *Drugs Aging* 5, 446-474 (1994); of clinical safety and efficacy in osteoporosis: T. P. van Staa *et al.*, *Pharmacotherapy* 18, 1121-1128 (1998).



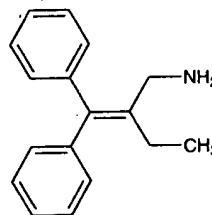
Crystallizes from water as the monohydrate. pK_1 1.35 ± 0.08; pK_2 2.87 ± 0.01; pK_3 7.03 ± 0.01; pK_4 11.3. Very sol in water (69% at 20° C). Insol in acetic acid.

Disodium salt. [7414-83-7] Disodium dihydrogen (1-hydroxyethylidene)bis[phosphonate]; etidronate disodium; Didronel; Diphos; Etidron. $C_2H_6Na_2O_7P_2$; mol wt 249.99. Crystallizes from water as the di- or tetrahydrate.

USE: Sequestering and chelating agent; scale and corrosion inhibitor.

THERAP CAT: Bone resorption inhibitor.

3895. Etifelmin. [341-00-4] 2-Diphenylmethylenebutylamine; 2-ethyl-3,3-diphenyl-2-propenylamine; EDPA; Na III. $C_{17}H_{19}N$; mol wt 237.34. C 86.03%, H 8.07%, N 5.90%. Prepn: Heinrich, Heiger, *DE 1122514* (1962 to Giuliani GmbH), C.A. 57, 733c (1962).

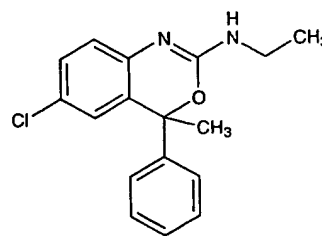


Hydrochloride. [1146-95-8] Tensinase D. $C_{17}H_{19}N.HCl$; mol wt 273.81. Crystals, mp 232°. Freely sol in water.

Mixture of hydrochloride and nicotinate. Gilutensin.

THERAP CAT: CNS stimulant; antihypotensive.

3896. Etifoxine. [21715-46-8] 6-Chloro-*N*-ethyl-4-methyl-4-phenyl-4*H*-3,1-benzoxazin-2-amine; 6-chloro-2-(ethylamino)-4-methyl-4-phenyl-4*H*-3,1-benzoxazine; HOE-36801. $C_{17}H_{17}ClN_2O$; mol wt 300.79. C 67.88%, H 5.70%, Cl 11.79%, N 9.31%, O 5.32%. Psychotropic agent with anxiolytic and anticonvulsant activity. Prepn: FR M7358; H. Kuch *et al.*, *US 3725404* (1969, 1973 both to Hoechst); I. Hoffmann *et al.*, *Arzneimittel-Forsch.* 20, 975 (1970). Exptl psychopharmacological study: J. R. Boissier *et al.*, *Therapie* 27, 325 (1972). Analysis of EEG effects: D. Bente *et al.*, *Arzneimittel-Forsch.* 25, 944 (1975). Evaluation of psychotropic effect: R. Corsico *et al.*, *Psychopharmacologia* 45, 301 (1976).



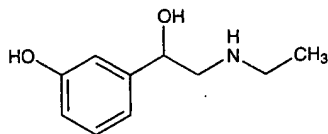
Colorless crystals from petr ether, mp 90-92°. uv max (ethanol): 273 nm (ϵ 21200). LD₅₀ orally in mice: 12 g/kg (Hoffmann).

Hydrochloride. [56776-32-0] Stresam. $C_{17}H_{17}ClN_2O.HCl$; mol wt 337.25. Crystals, mp 150-151°.

THERAP CAT: Anxiolytic.

3897. Etilefrin. [709-55-7] α -[(Ethylamino)methyl]-3-hydroxybenzenemethanol; α -[(ethylamino)methyl]-*m*-hydroxybenzyl alcohol; *m*-hydroxy- α -(ethylaminomethyl)benzyl alcohol; α -(*m*-hydroxyphenyl)- β -(ethylamino)ethanol; ethylphenylephrine; etiladrianol. $C_{10}H_{15}NO_2$; mol wt 181.23. C 66.27%, H 8.34%, N 7.73%, O 17.66%. Sympathomimetic amine. Prepn: T. Goto, *J. Pharm. Soc. Japan* 74, 318 (1954), C.A. 49, 3960 (1955); ES 273595 (1962 to Labs. Fher S.A.), C.A. 60, 1649e (1964). Clinical pharmacology: A. J. Coleman *et al.*, *Eur. J. Clin. Pharmacol.* 8, 41 (1975). Clinical pharmacokinetics and disposition: J. H. Hengstmann *et al.*, *ibid.* 9, 179 (1975). HPLC determin in plasma: K. Kojima *et al.*, *J. Chro-*

matog. 525, 210 (1990). Clinical trial in arterial hypotension: T. Taivainen, *Acta Anaesthesiol. Scand.* 35, 164 (1991); in neurocardiogenic syncope: F. Ammirati *et al.*, *Am. J. Cardiol.* 86, 472 (2000).



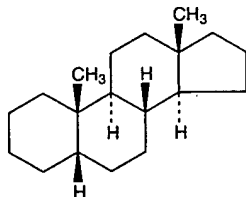
Crystals, mp 147-148°.

Hydrochloride. [534-87-2] Cardanat; Circupon; Effontil; Effortil; Efortil; Kertasin; Thomasin. $C_{10}H_{15}NO_2 \cdot HCl$; mol wt 217.70. Crystals, mp 121°. Bitter taste. Freely sol in water; sol in alcohol. Practically insol in chloroform.

THERAP CAT: Antihypotensive.

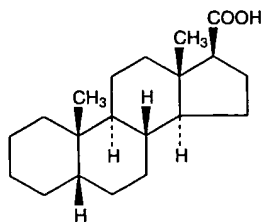
THERAP CAT (VET): Antihypotensive.

3898. Etiocolane. [438-23-3] (5 β)-Androstane; 5-epiandrosterone. $C_{19}H_{32}$; mol wt 260.46. C 87.62%, H 12.38%. Parent compd of alkyl substituted etiocholanes, such as pregnane, cholane, coprostane. Prep'd from etiocholane-17-one semicarbazone: Butenandt, Dannenbaum, *Z. Physiol. Chem.* 229, 192 (1934).



Needles from acetone, mp 78-80°.

3899. Etiocholanic Acid. [438-08-4] (5 β ,17 β)-Androstane-17-carboxylic acid; aetiocholanic acid; etianic acid; etiocholane-17 β -carboxylic acid. $C_{20}H_{32}O_2$; mol wt 304.47. C 78.90%, H 10.59%, O 10.51%. Prepn: Wieland *et al.*, *Z. Physiol. Chem.* 161, 80 (1926); Jacobs, Elderfield, *J. Biol. Chem.* 108, 497 (1935); Tschesche, *Ber.* 68, 9 (1935); Steiger, Reichstein, *Helv. Chim. Acta* 21, 841 (1938).



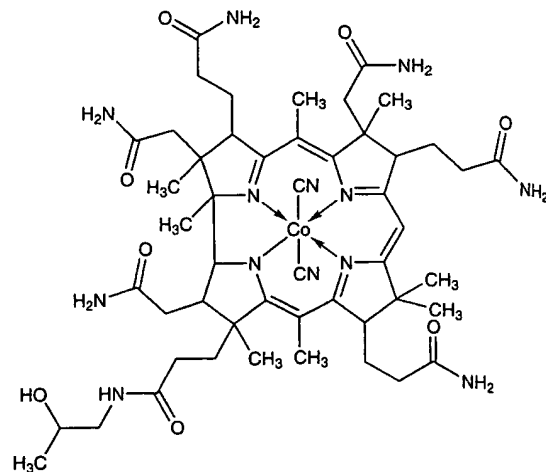
Needles from glacial acetic acid; elongated leaflets from acetic acid. Sublimes at 0.002 mm press. and 160° bath temp, mp 228-229°. Insol in water; sol in pentane.

Methyl ester. $C_{21}H_{34}O_2$. Needles from methanol, mp 99-101°.

Note: The stem name "etianic acid" was proposed by the Subcommittee on Steroid Nomenclature of the National Research Council as a replacement for "etiocholanic acid" in order to avoid the use of the same name for parent hydrocarbons of different carbon content: *J. Am. Chem. Soc.* 74, 2817 (1952).

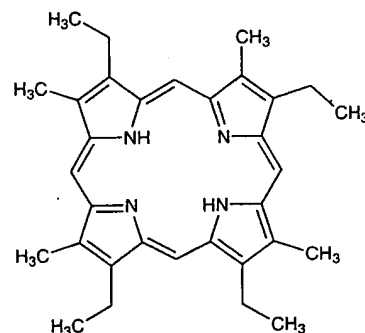
3900. Etiocobalamin. [27792-36-5] Cobinamide dicyanide; vitamin B_{12p}; Factor B. $C_{50}H_{72}CoN_{13}O_8$; mol wt 1042.12. C 57.63%, H 6.96%, Co 5.66%, N 17.47%, O 12.28%. Vitamin B₁₂ factor obtained by removal of the nucleotide from cyanocobalamin by acid hydrolysis. Isoln from calf feces: Ford, Porter, *Biochem. J.* 51, V (1952). Prepn by acid hydrolysis: Gant *et al.*, *ibid.* 56, XXXIV (1954); Friedrich, Bernhauer, *Angew. Chem.* 65, 627 (1953). Prepn from factor V_{1a} and D(-)-1-

amino-2-propanol: Bernhauer *et al.*, *Helv. Chim. Acta* 43, 1 (1960); Bernhauer, US 3072674 (1963 to Hoffmann-La Roche).



Note: The term etiocobalamin is used by some authors to designate any cobalamin lacking the nucleotide group present in vitamin B₁₂.

3901. Etioporphyrin. [26608-34-4] 2,7,12,18-Tetraethyl-3,8,13,17-tetramethyl-21H,23H-porphine; 1,3,5,8-tetramethyl-2,4,6,7-tetraethylporphine; etioporphyrin III; mesoetioporphyrin. $C_{32}H_{38}N_4$; mol wt 478.67. C 80.29%, H 8.00%, N 11.70%. Occurs in Bavarian oil shale, crude petr, ozokerite, Treibs, *Ann.* 510, 60 (1934); 517, 184 (1935); *Angew. Chem.* 49, 682 (1936). Prep'd by decarboxylation of mesoporphyrin Fischer, Treibs, *Ann.* 466, 191, 206 (1928). Synthesis: Fisch-Stangler, *Ann.* 462, 265 (1928); Johnson *et al.*, *J. Chem. Phys.* 1959, 3416. Structure: Abraham *et al.*, *ibid.* 1961, 3468. *Review:* Rimington, Kennedy, in M. Florkin, H. S. Mason, *Comparative Biochemistry* (Academic Press, New York, 1962), 557-614.



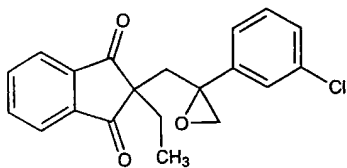
Long prismatic needles or butterflies from pyridine or chloroform-petr ether, mp 360-363°. pK_a 18. Absorption maxima: 246, 269, 396, 497, 532, 566, 620, 645 nm (log ϵ 3.90, 3.52, 4.13, 3.99, 3.81, 3.65, 2.62).

Copper salt. $C_{32}H_{36}N_4Cu$. Red needles from pyridine-acetic acid.

Magnesium salt. $C_{32}H_{36}N_4Mg$. Crystals from methanol.

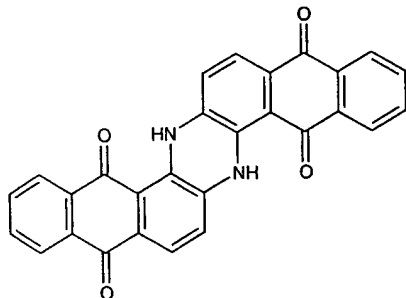
3902. Etiproston. [59619-81-7] (5Z)-7-[(1R,2R,3R,3',5'-Dihydroxy-2-[(1E)-2-[2-(phenoxy)methyl]-1,3-dioxolane-5-yl]ethenyl]cyclopentyl]-5-heptenoic acid; (5Z,13E)-(8R,11R,12R)-9,11-dihydroxy-15,15-ethylenedioxy-16-phenyl-17,18,19,20-tetranorprostadienoic acid; 15-deoxy-15,15-ethylenedioxy-16-phenoxy-17,18,19,20-tetranorprostaglandin. Prostavet; Vetiprost. $C_{24}H_{32}O_7$; mol wt 432.51. C 66.65%, H 7.46%, O 25.89%. Prostaglandin F_{2 α} analog with estrus synchronizing activity. Prepn: W. Skuballa *et al.*, *DE 2434 eide*, US 4088775 (1976, 1978 both to Schering AG);

or pressure at 25°: 2.8×10^{-6} Pa. LD₅₀ male, female rats (mg/kg): 631, 460 orally; >2000, >2000 dermally. LC₅₀ in rats (μl): 1.57 by inhalation (Yagi).



USE: Herbicide.

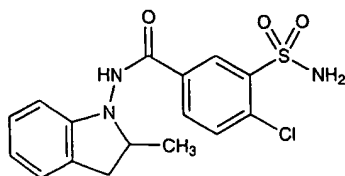
4959. Indanthrene®. [81-77-6] 6,15-Dihydro-5,9,14,18-thrazinetetrone; *N,N'*-dihydro-1,2,1',2'-anthraquinonazine. $C_{14}H_{14}N_2O_4$; mol wt 442.42. C 76.01%, H 3.19%, N 6.33%, O 4.7%. Vat dye discovered by René Bohn (1901). Prepn: Herz-David, Blangey, *Grundlegende Operationen der Farberemie* (Vienna, 5th ed., 1943) pp 304-305; Thielert, Bauman, *J. Pharm. Med.* **2693469** (1954 to Bayer); Sutter, Fioroni, *US 2831860* (1958 Ciba); Kastner, *US 3138612* (1964 to Allied Chem.). Structure: Weinstein, Merrit, *J. Am. Chem. Soc.* **81**, 3759 (1959).



Blue powder, dec 470-500°. uv max on cellophane film: 278 m. Practically insol in organic solvents. Sol in concd H_2SO_4 , in dil alkali solns. **Indanthrene Blue R**, the usual commercial grade, is extremely stable to light and heat, but sensitive to chlorine. A purer grade, which is not as sensitive to chlorine, is sold as **Indanthrene Brilliant Blue FF**.

USE: Mainly to dye cotton.

4960. Indapamide. [26807-65-8] 3-(Aminosulfonyl)-4-chloro-*N*-(2,3-dihydro-2-methyl-1*H*-indol-1-yl)benzamide; 4-chloro-*N*-(2-methyl-1-indolyl)-3-sulfamoylbenzamide; *N*-(3-sulfamoyl-4-chlorobenzamido)-2-methylindoline; S-1520; SE-1520; Bajaten; Damide; Fludex; Indaflex; Indamol; Ipamix; Loxol; Natrilix; Noranat; Tandix; Veroxil. $C_{16}H_{16}ClN_3O_3S$; mol wt 365.84. C 52.53%, H 4.41%, Cl 9.69%, N 11.49%, O 13.12%, S 8.76%. Prepn: Beregi *et al.*, *FR 2003311*; *idem*, *US 3565911* (1969, 1971, both to Sci. Union et Cie, Soc. Franc. Recherche Med.). Pharmacology: Leary *et al.*, *Curr. Ther. Res. Clin. Exp.* **15**, 571 (1973); D. B. Campbell, R. A. Moore, *Postgrad. Med. J., Suppl.* **57**, 7 (1981). Acute toxicity data: J. Kyncl *et al.*, *Arzneimittel-Forsch.* **25**, 1491 (1975). Symposium on pharmacology and clinical efficacy: *Am. J. Med.* **84**, Suppl. 1B, 1-111 (1988); *Am. J. Cardiol.* **65**, Suppl. H, 1H-80H (1990). Comprehensive description: T. J. DiFeo, J. E. Shuster, *Anal. Profiles Drug Subs. Excerpt.* **23**, 229-268 (1994).



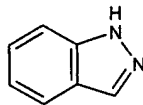
Crystals from isopropanol/water, mp 160-162°. uv max (methanol): 242, 278, 286 nm ($A_{1cm}^{1\%}$ 630, 98, 100). Sol in meth-

anol, acetic acid, ethyl acetate. Very slightly sol in chloroform. pKa (25°) 8.8 ± 0.2 . LD₅₀ in rats, mice, guinea pigs (mg/kg): 393-421, 410-564, 347-416 i.p.; 394-440, 577-635, 272-358 i.v.; >3000 all species orally (Kyncl).

Hemihydrate. Pressural. $C_{16}H_{16}ClN_3O_3S \cdot \frac{1}{2}H_2O$; mol wt 374.85.

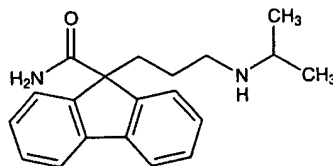
THERAP CAT: Antihypertensive; diuretic.

4961. 1*H*-Indazole. [271-44-3] Isoindazole; benzo-pyrazole. $C_7H_6N_2$; mol wt 118.14. C 71.17%, H 5.12%, N 23.71%. Prepn: Stephenson, *Org. Syn., coll. vol. III*, 475 (1955); Ainsworth, *Org. Syn.* **39**, 27 (1959); Huisgen, Bast, *ibid.* **42**, 69 (1962).



Needles from hot water, mp 146.5°. bp₇₄₃ 267-270°. Sol in hot water, alcohol, ether.

4962. Indecainide. [74517-78-5] 9-[3-[(1-Methylethyl-amino)propyl]-9*H*-fluorene-9-carboxamide; 9-carbamoyl-9-(3-isopropylaminopropyl)fluorene; 9-[3-(isopropylamino)propyl]-9-(aminocarbonyl)fluorene; ricainide. $C_{20}H_{24}N_2O$; mol wt 308.42. C 77.89%, H 7.84%, N 9.08%, O 5.19%. Prepn: W. B. Lacefield, R. L. Simon, *US 4197313* and *US 4452745* (1980, 1984 both to Lilly). Pharmacokinetics in animals: T. L. Lindstrom, G. W. Whitaker, *Drug Metab. Dispos.* **12**, 683 (1984). Metabolism: *idem*, *ibid.* 691. LC determ in biological fluids: K. Z. Farid *et al.*, *J. Chromatog.* **337**, 329 (1985). Toxicological studies: G. E. Sandusky, Jr., D. B. Meyers, *Fundam. Appl. Toxicol.* **5**, 175 (1985). Clinical evaluation in cardiac arrhythmias: P. F. Nestico *et al.*, *Am. J. Cardiol.* **59**, 1332 (1987); P. J. Podrid *et al.*, *ibid.* **61**, 764 (1988).

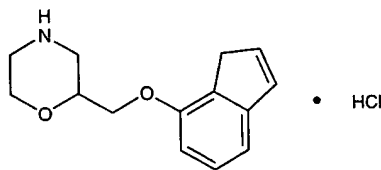


Crystals from Skelly B, mp 94-95°.

Hydrochloride. [73681-12-6] LY-135837; Decabid. $C_{20}H_{24}N_2O \cdot HCl$; mol wt 344.89. Crystals from chloroform, mp 216.5-217°; also reported as crystals from fresh ethanol and diethyl ether, mp 203-204°. LD₅₀ orally in male, female mice, rats: 100, 96, 103, 82 mg/kg (Sandusky, Meyers).

THERAP CAT: Antiarrhythmic (cardiac depressant).

4963. Indeloxazine Hydrochloride. [65043-22-3] 2-[(1*H*-Inden-7-yloxy)methyl]morpholine hydrochloride; (±)-2-[(7-indenyloxy)methyl]morpholine hydrochloride; YM-08054-1; Elen; Noin. $C_{14}H_{18}ClNO_2$; mol wt 267.76. C 62.80%, H 6.78%, Cl 13.24%, N 5.23%, O 11.95%. Serotonin uptake inhibitor. Prepn: M. Masuo *et al.*, *DE 2601703*; *idem*, *US 4109088* (1976, 1978 both to Yamanouchi). Synthesis and resolution of isomers: T. Kojima *et al.*, *Chem. Pharm. Bull.* **33**, 3766 (1985). Pharmacology and toxicity: S. Tachikawa *et al.*, *Arch. Int. Pharmacodyn.* **238**, 81 (1979). Inhibition of synaptosomal uptake of serotonin and noradrenaline: M. Harada, H. Maeno, *Biochem. Pharmacol.* **28**, 2645 (1979). GLC determ in human plasma: A. G. Hayes, T. Chang, *J. Chromatog.* **272**, 176 (1983).

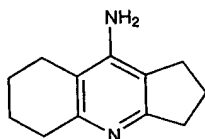


maceutical preparations by HPLC: D. A. Elvidge *et al.*, *J. Chromatog.* **463**, 107 (1989). Review of distribution and chemistry of ipecac alkaloids: M.-M. Janot in *The Alkaloids*, vol. 3, R. H. F. Manske, H. L. Holmes, Eds. (Academic Press, New York, 1953) pp 363-394; A. Brossi, S. Teitel, *ibid.* vol. 13, 189-212 (1971). Review of use in acute poisoning: W. D. King, *Clin. Toxicol.* **17**, 353-358 (1980).

THERAP CAT: Emetic; expectorant.

THERAP CAT (VET): Emetic; expectorant.

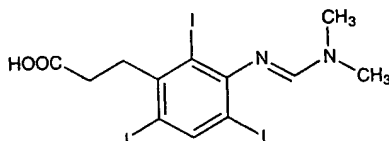
5089. Ipidacrine. [62732-44-9] 2,3,5,6,7,8-Hexahydro-1*H*-cyclopenta[*b*]quinolin-9-amine; 9-amino-2,3,5,6,7,8-hexahydro-1*H*-cyclopenta[*b*]quinoline; amiridin. $C_{12}H_{16}N_2$; mol wt 188.27. C 76.55%, H 8.57%, N 14.88%. Cholinesterase inhibitor; structural analog of tacrine, *q.v.* Prepn: A. V. Upadysheva *et al.*, *Khim.-Farm. Zh.* **11**, 40 (1977), *C.A.* **86**, 189676q (1977). Prepn of the hydrochloride monohydrate: E. F. Levretskaya *et al.*, *DE 3231571*; *eidem*, *US 4550113* (1984, 1985 both to Sci. Res. Inst. Biol. Test. Chem. Compds). Neuropharmacology: T. Nabeshima *et al.*, *Eur. J. Pharmacol.* **154**, 263 (1988). Anticholinesterase activity: S. Shibasaki *et al.*, *Pharmacol. Biochem. Behav.* **39**, 499 (1991). Clinical evaluation in Alzheimer's disease: E. E. Bukatina *et al.*, *Neurosci. Behav. Physiol.* **23**, 83 (1993).



Hydrochloride. [90043-86-0]; [118499-70-0] (monohydrate. NIK-247. $C_{12}H_{16}N_2 \cdot HCl$; mol wt 224.74. Prepd as the monohydrate. White or slightly creamy, odorless powder. Readily sol in water, dil acids; slowly sol in ethanol. Practically insol in acetone, ether, chloroform.

THERAP CAT: Nootropic.

5090. Ipodate. [5587-89-3] 3-[[[Dimethylamino)methylene]amino]-2,4,6-triiodobenzenepropanoic acid; 3-[[[dimethylaminomethylene]amino]-2,4,6-triiodohydrocinnamic acid; 2,4,6-triiodo-3-[[[dimethylaminomethylene]amino]hydrocinnamic acid; β -(3-dimethylaminomethyleneamino-2,4,6-triiodophenyl)propionic acid. $C_{12}H_{13}I_3N_2O_2$; mol wt 597.96. C 24.10%, H 2.19%, I 63.67%, N 4.68%, O 5.35%. Prepn: Prieve, Poljak, *Ber.* **93**, 2347 (1960). Toxicity data: J. O. Hoppe *et al.*, *J. Med. Chem.* **13**, 997 (1970).



Crystals, mp 168-169° (dec 225°). Practically insol in water. Very sol in methanol, ethanol, chloroform, acetone, dil sulfuric acid. Estimated pK 5-5.5.

Sodium salt. [1221-56-3] Sodium ipodate; Biloptin; Ora-grafin Sodium. $C_{12}H_{12}I_3N_2NaO_2$; mol wt 619.94. Bitter leaflets from water + acetone, mp 303-304° (decompn with evolution of iodine). Very freely sol in water; freely sol in methanol, ethanol. Practically insol in acetone, ether. Soly in DMF and DMSO about 33 g/100 ml; in dimethylacetamide about 66 g/100 ml. LD_{50} in mice (mg/kg): 290 i.v.; 2570 orally (Hoppe).

Calcium salt. [1151-11-7] Calcium ipodate; Solu-Biloptin; Ora-grafin Calcium. $C_{24}H_{24}CaI_6N_4O_4$; mol wt 1233.98. Crystals, mp 298-302°. Soly in water at 20°: 0.1%. Sol in chloroform, dimethylformamide, hot propylene glycol.

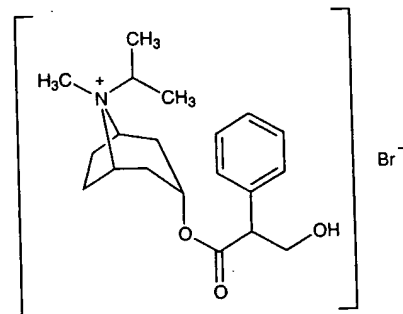
Ethyl ester. SH-617L. $C_{14}H_{17}I_3N_2O_2$; mol wt 626.01.

THERAP CAT: Diagnostic aid (radiopaque medium—cholecystographic).

5091. Ipomea. Mexican scammony (root); Orizaba jalap root. Dried root of *Ipomoea orizabensis* Ledenois, *Convolvulaceae*. Active constituent is the resin. Yields not less than 15% total ipomea resins. Different from *Ipomoea violacea* var. *Pearly Gates* Hort., *Convolvulaceae* and *Ipomoea rubrocoerulea* var. *praecox*, *morning-glory*, *ololiuqui*, which contain ergot alkaloids. Occurrence of lysergic acid derivatives and of ergolines in Ipomea: A. Hofmann, H. Tschertler, *Experientia* **16**, 414 (1960); D. Stauffacher *et al.*, *Helv. Chim. Acta* **48**, 1379 (1965).

THERAP CAT: Cathartic.

5092. Ipratropium Bromide. [22254-24-6] (3-endo,8-syn)-3-(3-Hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide; 3 α -hydroxy-8-isopropyl-1 α H,5 α H-tropanium bromide (\pm)-tropate; 8-isopropylnoratropine methobromide; *N*-isopropylnoratropinium bromomethylate; Sch-1000; Atem; Atrovent; Bitrop; Itrop; Narilet; Rinatoc. $C_{20}H_{30}BrNO_3$; mol wt 412.37. C 58.25%, H 7.33%, Br 19.38%, N 3.40%, O 11.64%. Anticholinergic. Prepn: K. Zeile *et al.*, *ZA 67 07766*; *eidem*, *US 3505337* (1968, 1970, both to Boehringer, Ing.); W. Schulz *et al.*, *Arzneimittel-Forsch.* **26**, 960 (1976). Chemistry and pharmacokinetics: W. Deckers, *Postgrad. Med. J.* **51**, Suppl. 7, 76 (1975). Pharmacology and toxicology: A. Engelhardt, H. Klupp, *ibid.* 82. Series of articles on pharmacology, toxicology, pharmacokinetics and clinical studies: *Arzneimittel-Forsch.* **26**, 974-985, 989, 1020 (1976). Toxicity data: L. Sarafana *et al.*, *ibid.* 985. Review: R. Bauer *et al.*, in *Pharmacological and Biochemical Properties of Drug Substances* vol. 2, M. E. Goldberg, Ed. (Am. Pharm. Assoc., Washington, DC, 1979) pp 489-515. Symposium on pharmacology, toxicology and clinical efficacy: *Am. J. Med.* **81**(5A), 1-102 (1986). Review of clinical toxicology: J. D. Truitt, *Crit. Care Clinics* **7**, 639-657 (1991).



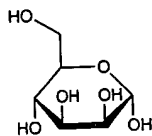
White crystals from *n*-propanol, mp 230-232°. Freely sol in water and lower alcohols. Insol in ether, chloroform and fluoro-hydrocarbons. Fairly stable in neutral and acid solns; rapidly hydrolyzed in alkaline soln. LD_{50} in male, female mice (mg/kg): 1001, 1083 orally; 12.29, 14.97 i.v.; 300, 340 s.c. LD_{50} in male, female rats (mg/kg): 1663, 1779 orally; 15.89, 15.70 i.v. (Sarafana).

THERAP CAT: Bronchodilator; antiarrhythmic.

5093. Ipriflavone. [35212-22-7] 7-(1-Methylethoxy)-3-phenyl-4*H*-1-benzopyran-4-one; 7-isopropoxy-3-phenyl-4*H*-1-benzopyran-4-one; 7-isopropoxy-3-phenylchromone; 7-isopropoxyisoflavone; FL-113; TC-80; Iprostren; Osteofix; Yambolap. $C_{18}H_{16}O_3$; mol wt 280.32. C 77.12%, H 5.75%, O 17.12%. Isoflavone derivative with anti-anginal and anti-osteopenic activity. Prepn: L. Feuer *et al.*, *DE 2125245* (1971 to Chinoin), *C.A.* **76**, 72407e (1972). Use as anabolic in animals: *eidem*, *US 3833730*; in humans; *eidem*, *US 3949085* (1974, 1976 both to Chinoin). Cardiovascular properties in stable angina: V. Grubich *et al.*, *Lancet* **1**, 211 (1979). Cardio-logical effects in animals: L. Feuer *et al.*, *Arzneimittel-Forsch.* **31**, 953 (1981). Metabolism and disposition in rats: K. Yoshida *et al.*, *Radioisotopes* **34**, 612, 618 (1985). Effect in rats on estrogen-stimulated calcitonin secretion: I. Yamazaki, *Life Sci.* **38**, 757 (1986); I. Yamazaki, M. Kinoshita, *ibid.* 1535; on glucocorticoid-induced osteoporosis: I. Yamazaki *et al.*, *ibid.* 951.

sol in ethanol. Aq solns are mildly acidic and stable at emps. Claimed to be considerably less toxic than mechamine. LD₅₀ i.v. in rats: 56 mg/kg (Scherf).
THERAP CAT: Antineoplastic.

12. D-Mannose. [3458-28-4] Seminose; carubinose. C₆H₁₂O₆; mol wt 180.16. C 40.00%, H 6.71%, O 53.28%. of α-form by treating ivory nut shavings with H₂SO₄: *J. Res. Nat. Bur. Stand.* **26**, 47 (1941); Isbell, Frush in *eds in Carbohydrate Chemistry*, R. L. Whistler, M. L. Wol-Eds. (Academic Press, New York, 1962) pp 145-147. and stability of α- and β-forms: Reeves, *J. Am. Chem.* **72**, 1499 (1950); J. Sowden in *The Carbohydrates*, W. Pig-Ed. (Academic Press, New York, 1957) pp 94-95.



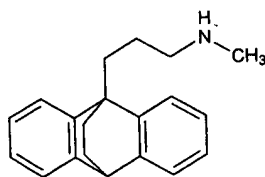
α-D-Mannose

Form. Crystals from methanol, mp 133°. [α]_D +29.3° → 1.2° (water).

Form. Orthorhombic, bisphenoidal needles from alcohol acetic acid, dec 132°. Sweet taste with bitter aftertaste. d₂₀ 1.4. Shows mutarotation. [α]_D²⁰ -17.0° → +14.2° (c = 4). 1 gram dissolves in 0.4 ml water, 120 ml methanol, 250 ml ethanol, 3.5 ml pyridine. pK_a (18°): 11.98. Reduces Fehling's soln; is fermented by yeast.

Phenylhydrazone. C₁₂H₁₈N₂O₅. Crystals from dil ethanol, mp 199-200°. [α]_D²⁰ +26.3° → +33.8° (pyridine).
CaCl₂-addition compd tetrahydrate. C₆H₁₂O₆·CaCl₂·4H₂O. mp 101-102°. [α]_D²⁰ -31.3° → +6.0° (c = 9).

5773. Maprotiline. [10262-69-8] *N*-Methyl-9,10-ethanoanthracene-9(10*H*)-propanamine; 9-(γ-methylaminopropyl)-10-dihydro-9,10-ethanoanthracene; 1-(3-methylaminopropyl)-10-phenyl-10,10-dihydro-9,10-ethanoanthracene. C₂₀H₂₃N; mol wt 277.40. C 86.59%, H 8.36%, N 5.05%. Prepn: P. Schmidt *et al.*, *US* **399201** (1968 to Ciba). Synthesis, NMR, mass spectra: M. Vilhelm, P. Schmidt, *Helv. Chim. Acta* **52**, 1385 (1969). Toxicity: R. Hess *et al.*, *Boll. Chim. Farm.* **112**, 782 (1973), *C.A.* **81**, 33479p (1974). Review of pharmacology and therapeutic efficacy: R. M. Pinder *et al.*, *Drugs* **13**, 321 (1977). Comprehensive description: S. K. Suh, J. B. Smith, *Anal. Profiles Drug Subs.* **15**, 393-426 (1986).

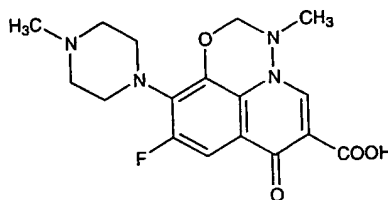


mp 92-94°.

Hydrochloride. [10347-81-6] Ba-34276; Depilept; Ludiomil; Pymion. C₂₀H₂₃N·HCl; mol wt 313.87. Crystals from isopropanol, mp 230-232°. Freely sol in methanol and chloroform, slightly sol in water. Practically insol in isooctane. LD₅₀ in mice, rats (mg/kg): ~750, ~900 orally (Hess).
THERAP CAT: Antidepressant.

5774. Marbofloxacin. [115550-35-1] 9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido-[3,2,1-*ij*][4,1,2]benzoxadiazine-6-carboxylic acid; Marbocyl. C₁₇H₁₉FN₄O₄; mol wt 362.35. C 56.35%, H 5.28%, F 5.24%, N 15.46%, O 17.66%. Fluorinated quinolone antibacterial. Prepn: M. Aoki *et al.*, *EP* **259804**; K. Yokose *et al.*, *US* **4801584** (1987, 1989 both to Hoffmann-LaRoche). HPLC determination in plasma: M. A. Garcia *et al.*, *J. Chromatog. B* **729**, 157 (1999). Evaluation of experimental surgical infection in dogs: P. Gruet *et al.*, *Vet. Rec.* **140**, 199 (1997). Pharmacokinetics and

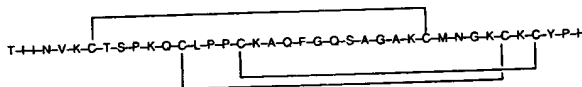
efficacy in cattle: C. Eyett-Burton *et al.*, *Cattle Practice* **5**, 289 (1997). Pharmacokinetics in renally impaired dogs: H. P. LeFebvre *et al.*, *J. Vet. Pharmacol. Ther.* **21**, 453 (1998).



Crystals from methanol, mp 268-269° (dec).
THERAP CAT (VET): Antibacterial.

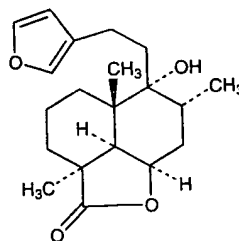
5775. Margaric Acid. [506-12-7] Heptadecanoic acid. C₁₇H₃₄O₂; mol wt 270.45. C 75.50%, H 12.67%, O 11.83%. CH₃(CH₂)₁₅COOH. Prepn: Kaufmann, Stamm, *Ber.* **91**, 2121 (1958); Bhattacharyya *et al.*, *Chem. & Ind. (London)* **1959**, 1352; Hünig, Ledle, *Ber.* **93**, 913 (1960). Metabolism: Boyer, Scheig, *Lipids* **4**, 615 (1969). Toxicity study: L. Orö, A. Wretling, *Acta Pharmacol. Toxicol.* **18**, 141 (1961). Crystals from alcohol, mp 61°. d 0.853. bp₁₀₀ 227°. n_D²⁰ 1.4342. Insol in water. Freely sol in ether; slightly sol in alcohol. LD₅₀ i.v. in mice: 360.3 mg/kg (Orö, Wretling).

5776. Margatoxin. [145808-47-5] MgTX. C₁₇₈H₂₈₆N₅₂O₅₀S₇; mol wt 4179.02. C 51.16%, H 6.90%, N 17.43%, O 19.14%, S 5.37%. Peptide toxin isolated from the new world scorpion, *Centruroides margaritatus*, consists of 39 amino acids with 3 disulfide bridges. Selectively inhibits voltage-gated potassium channels. Isolation and characterization: M. Garcia-Calvo *et al.*, *J. Biol. Chem.* **268**, 18866 (1993). Synthesis: M. A. Bednarek *et al.*, *Biochem. Biophys. Res. Commun.* **198**, 619 (1994). NMR determination of three dimensional structure: B. A. Johnson *et al.*, *Biochemistry* **33**, 15061 (1994). Use as an affinity label for potassium channels: H.-G. Knaus *et al.*, *ibid.* **34**, 13627 (1995); H. S. Fischer, A. Saria, *Neurosci. Letters* **263**, 208 (1999).

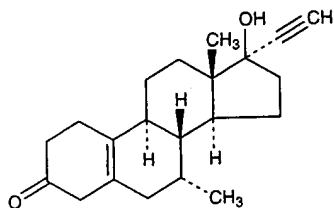


USE: Biochemical probe.

5777. Marrubiin. [465-92-9] [2a*S*-(2α,5α,6α,7α,8α,8βα)]-6-[2-(3-Furanyl)ethyl]decahydro-6-hydroxy-2a,5a,7-trimethyl-2*H*-naphtho[1,8-*bc*]furan-2-one; 15,16-epoxy-6β,9-dihydroxy-8β*H*-labda-13(16),14-dien-19-oic acid γ-lactone; 5-[2-(3-furyl)ethyl]decahydro-5,8-dihydroxy-1,4a,6-trimethyl-1-naphthoic acid γ-lactone. C₂₀H₂₈O₄; mol wt 332.43. C 72.26%, H 8.49%, O 19.25%. Diterpene lactone principle isolated from white horehound, *Marrubium vulgare* (Tourm.) L., *Labiatae*: Harms, *Arch. Pharm.* **83**, 144 (1842); Ludwig, Kromayer, *ibid.* **158**, 257 (1861); Nicholas, *J. Pharm. Sci.* **53**, 895 (1964). Alternate view that marrubiin is an artefact generated from *pre-marrubiin* during the isolation: Henderson, McCrindle, *J. Chem. Soc. (C)* **1969**, 2014. Structure and stereochemistry: Cocker *et al.*, *J. Chem. Soc.* **1953**, 2540; *Chem. & Ind. (London)* **1954**, 1561; **1955**, 1484; Fulke, McCrindle, *ibid.* **1965**, 647. Total stereochemistry: Wheeler *et al.*, *Tetrahedron* **23**, 3909 (1967); Appleton *et al.*, *J. Chem. Soc. (C)* **1967**, 1943. Synthesis: Mangoni *et al.*, *Tetrahedron* **28**, 611 (1972).



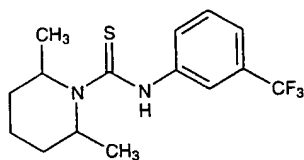
17 β -hydroxy-19-norandrost-5(10)-en-3-one; 7 α -methylethynyl-17 β -hydroxyestr-5(10)-en-3-one; Org-OD-14; C₂₁H₂₈O₂; mol wt 312.44. C 80.73%, H 9.03%, O 9.24%. Synthetic steroid with weak estrogenic, androgenic and oestrogenic activity. Prepn: NL 6406797; H. P. de N. P. van Vliet, US 3340279 (1965, 1967 both to Organon). Improved process: M. S. de Winter, E. A. Harryvan, 75465 (1969 to Organon). Endocrinological profile: J. Ser *et al.*, *Arzneimittel-Forsch.* **34**, 1010 (1984). Series of studies on pharmacology and clinical efficacy in post-menopausal women: *Maturitas* Suppl 1, 1-72 (1987). Clinical effect on osteoporosis: P. Geusens *et al.*, *ibid.* **13**, 155 (1991).



Crystals, mp 165-169°.

HERAP CAT: In treatment of menopausal syndrome.

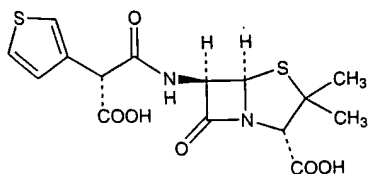
9504. **Ticarbodine**. [31932-09-9] 2,6-Dimethyl-N-[3-(trimethylphenylthio)-1-piperidinecarboxy]-m-toluidide; EL-Tribodine. C₁₅H₁₉F₃N₂S; mol wt 316.39. C 56.94%, H 5.91%, F 18.01%, N 8.85%, S 10.13%. Deriv of thiourea, q.v. n: H. D. Porter, H. M. Taylor, US 3659012 (1972 to Lilly). Anthelmintic efficacy in dogs: R. J. Boisvenue *et al.*, *Am. J. Res.* **33**, 709 (1972); G. F. Slonka *et al.*, *ibid.* 1075; D. K. Collins, *Proc. Helminthol. Soc. Wash.* **43**, 135 (1978).



Light yellow cryst, mp 123-126°.

HERAP CAT (VET): Anthelmintic.

9505. **Ticarcillin**. [34787-01-4] (2S,5R,6R)-6-[[[(2R)-Carboxy-3-thienylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid; N-(2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-6-yl)-3-thienylacetophenemalonamic acid; 6-[D(-)- α -carboxy-3-thienylacetophenyl]penicillanic acid; α -carboxy-3-thienylmethylpenicillin. C₁₈H₁₆N₂O₆S₂; mol wt 384.43. C 46.87%, H 4.20%, N 7.29%, S 16.97%, S 16.68%. Broad spectrum semi-synthetic antibiotic related to penicillin. Prepn: BE 646991; E. G. Brain, J. H. Ayler, US 3282926 (1964, 1966 to Beecham Group Ltd.). In vitro studies: H. C. Neu, E. B. Winshell, *Antimicrob. Ag. Chemother.* **1970**, 385; R. Sutherland *et al.*, *ibid.* 390; N. J. Egakis, J. Papavassiliou, *J. Antibiot.* **28**, 912 (1975). In vivo studies: P. Acred *et al.*, *Antimicrob. Ag. Chemother.* **1970**, 396. Absorption and excretion: R. Sutherland, P. J. Wise, *ibid.* 402. Clinical pharmacology: V. Rodriguez *et al.*, *Antimicrob. Ag. Chemother.* **4**, 31 (1973); R. D. Libke *et al.*, *Clin. Pharmacol. Ther.* **17**, 441 (1975). Review of pharmacology and therapeutic efficacy: R. N. Brogden *et al.*, *Drugs* **20**, 325-352 (1980).

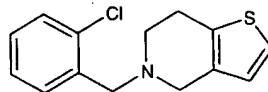


Disodium salt. [4697-14-7] BRL-2288; Aerugipen; Monapen; Ticar; Ticarpen; Ticillin. C₁₅H₁₄N₂Na₂O₆S₂; mol wt 428.40. Creamy-white hygroscopic non-crystalline powder. Readily sol in water (>100 g/100 ml water) giving a clear soln with pH between 6.0 and 8.0. Aq solns are relatively stable; acid solns relatively unstable (Sutherland).

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antibacterial.

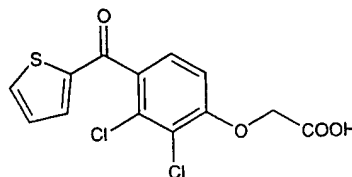
9506. **Ticlopidine**. [55142-85-3] 5-[(2-Chlorophenyl)methyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine; 5-(o-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine. C₁₄H₁₄ClNS; mol wt 263.79. C 63.75%, H 5.35%, Cl 13.44%, N 5.31%, S 12.16%. Platelet aggregation inhibitor. Prepn: DE 2404308; A. R. J. Castaigne, US 4051141 (1974, 1977 both to Cent. Etudes Ind. Pharm.); E. Braye, US 4127580 (1978 to Parcor). Metabolism: P. Godard *et al.*, *Eur. J. Drug Metab. Pharmacokinet.* **3**, 67 (1978); *eidem*, *ibid.* **4**, 133 (1979); A. Tuong *et al.*, *ibid.* **6**, 91 (1981). Mode of action: G. Leblondel, P. Allain, *Biochem. Pharmacol.* **27**, 2099 (1978); J. R. O'Brien *et al.*, *Thromb. Res.* **13**, 245 (1978); J. J. Bruno, *ibid.* **1983**, Suppl. 4, 59. Pharmacology: A. Akashi *et al.*, *Arzneimittel-Forsch.* **30**, 409, 415 (1980). Clinical studies: J. J. Thebault *et al.*, *J. Int. Med. Res.* **5**, 405 (1977); C. Lecrubier *et al.*, *Therapie* **32**, 189 (1977); T. Katsumura *et al.*, *Angiology* **33**, 357 (1982). Review of pharmacodynamics, pharmacokinetics and therapeutic use: E. Saltiel, A. Ward, *Drugs* **34**, 222-262 (1987). Comprehensive description: F. J. Al-Shammary, N. A. A. Mian, *Anal. Profiles Drug Subs. Excip.* **21**, 573-609 (1992).



Hydrochloride. [53885-35-1] 4-C-32; 53-32 C; Anagregal; Caudaline; Panaldine; Ticlid; Ticlodix; Ticlodone; Ticlosin; Tiklid. C₁₄H₁₄ClNS.HCl; mol wt 300.25. Crystals from ethanol, mp 190°. uv max (water): 214, 268, 295 nm (A_{1cm}^{1%} 303.8, 13.14, 2). pKa 7.64. Almost sol in water; sol in 95% alcohol, methanol, chloroform. Insol in ether. LD₅₀ in mice (mg/kg/24 hrs): 55 i.v.; >300 orally (Castaigne).

THERAP CAT: Antithrombotic.

9507. **Ticrynafen**. [40180-04-9] [2,3-Dichloro-4-(2-thienylcarbonyl)phenoxy]acetic acid; [2,3-dichloro-4-(2-thenoyl)phenoxy]acetic acid; [2,3-dichloro-4-(2-thiophenecarbonyl)phenoxy]acetic acid; tienilic acid; thienylic acid; ANP-3624; CE-3624; SKF-62698; Diflurex; Selacryn. C₁₃H₈Cl₂O₄S; mol wt 331.17. C 47.15%, H 2.44%, Cl 21.41%, O 19.32%, S 9.68%. A heterocyclic derivative of phenoxyacetic acid. Prepn: J. Godfroid, J. Thuillier, DE 2048372; US 3758506 (1971, 1973 both to C.E.R.P.H.A.) and FR 2115042 (1972 to C.E.R.P.H.A.). Synthesis and pharmacology: G. Thuillier *et al.*, *Eur. J. Med. Chem.* **9**, 625 (1974). Pharmacokinetics in healthy volunteers: A. L. Kerremans *et al.*, *Eur. J. Clin. Pharmacol.* **22**, 515 (1982). Comparative study in hypertensive patients: B. T. Emmerson *et al.*, *ibid.* 203. Hepatotoxicity study: J. W. Manier *et al.*, *Am. J. Gastroenterol.* **77**, 401 (1982).



Crystals from 50% ethanol, mp 148-149°; also reported as mp 157°. LD₅₀ in mice (mg/kg): 225 i.v., 1275 orally (US 3758506).

THERAP CAT: Diuretic; uricosuric; antihypertensive.

9508. **Tiemonium Iodide**. [144-12-7] 4-[3-Hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methylmorpholinium iodide; N-

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